REMARKS

Claims 1-7 and 15-24 are pending in the application. Claims 8-14 were drawn to a nonelected invention. Claims 8-14 have been canceled without prejudice to filing a divisional application directed to the canceled claims.

Claim 1 has been amended to clarify Applicants' invention. Support for this amendment can be found in the specification at, for example, page 4, lines 24 - 35 and at page 22. Claim 5 has been amended to correct a grammatical error resulting from a previous claim amendment. The amendment places the claim into better condition for allowance. No new matter is added by way of the amendments.

Withdrawn Rejection

Applicants gratefully acknowledge the withdrawal of the objection to claim 5.

Applicants gratefully acknowledge the withdrawal of the rejections of claims 3-7 and 15-16 under 35 U.S.C. §112, first paragraph (enablement).

Applicants gratefully acknowledge the withdrawal of the rejection of claim 5 under 35 U.S.C. §112, first paragraph (written description).

Rejection of Claims 1-2 under 35 U.S.C. §112, first paragraph

Claims 1-2 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The claims contain subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

Specifically, undue experimentation would allegedly be required by one skilled in the art to identify a patient population in need of increased active IGF-I levels. The claims allegedly fail to recite limitations as to specific mammals that are in need of increased IGF-I levels (page 4 of office action). The numerous disorders, diseases and conditions encompassed by the claims have

different pathophysiologies and one skilled in the art would not be able to predict from the instant specification that an IGF-I variant recited in the claims would be able to treat all possible patient populations that exhibit a need for increasing active IGF-I levels (page 5 of the office action).

This rejection is traversed for the following reasons.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [1] [2]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[4] [5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[6] [7]. "Limitations and examples in the specification do not generally limit what is covered by the claims"[8]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It

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[1] MPEP §2164.0120

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))
United States v. Telectronics, Inc. 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[5] MPEP §2164.06.

[6] MPEP §2164.08

[7] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

[8] MPEP § 2164.08

is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[9]

The Disclosure provides sufficient information to enable the claimed invention

Claim 1 recites methods for increasing active IGF-I levels in a mammal having a lower level of active IGF-I relative to the level in a normal mammal, by administering to a mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of the native sequence human IGF-I are replaced with an alanine, a glycine or a serine residue.

The Office Action states that one would not be able to identify a patient population in need of increased IGF-I levels.

The Office acknowledges that the specification of the instant application discloses that disease states characterized by low IGF-bioactivity include hyperglycemic disorders, renal disorders, congestive heart failure, hepatic failure, poor nutrition, Turner's syndrome etc. (page 11, lines 27-35 through page 12, lines 1-5). The office acknowledges that WO98/45427 teaches that diseases associated with a lack of active IGF-I in the bloodstream include diabetes, obesity, anabolic disorders, immunologic disorders, cardiac disorders and renal disorders (pg 44, lines 9-10). Clearly there is sufficient disclosure of diseases which are characterized by having low active IGF-I. One skilled in the art would know to look in the population of patients having these diseases for those patients having low active IGF-I.

Furthermore, undue experimentation would not be required to identify individuals with reduced IGF-I levels. Determination of levels of active IGF-I, IGFBP-1 and IGFBP-3 can be done through standard clinical means, for example ELISA for levels of molecules, clinical

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[9] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

chemistry RIA or bioassay. See, for example page 22, lines 11 – 30, which describe methods for measuring the level of active IGF-I levels. See also Example 3, page 41-42 which describes measurements of IGF-I in rats and Example 4, pages 42-43, International Patent Application No. WO98/45427, and U.S. Patent No. 5,565,428, both published before the effective filing date, which describe methods of measuring IGF-I, IGFBP-1 and IGFBP-3. Thus, one skilled in the art based on the disclosure in the specification and the cited patent disclosures would know how to measure levels of IGF-I, IGFBP-1 and IGFBP-3 in patients and identify those patients having low active IGF-I levels.

For the reasons set forth above, one skilled in the art would be readily able to identify the patient population with low active IGF-I levels.

The Office action states that one of skill in the art would not be able to predict from the instant specification that an IGF-I variant would be able to treat all possible patient populations that exhibit a need for increasing active IGF-I levels. Applicants respectfully disagree.

First Applicants note that Claims 1 and 2 are directed to a method of "increasing active IGF-I levels in a mammal". Secondly, the definition of "treat" in the specification includes both therapeutic treatment and prophylactic or preventative measures. Thus the claims are directed to raising the level of active IGF-I in the patient, which patient may have any of the recited diseases or disorders.

Secondly, Applicants describe precisely the IGF-I variants of the claimed invention and show that the variants bind IGFBP-1 very weakly while retaining high affinity binding of IGFBP-3. See for example, Example 1, page 27-38 and Tables I and II. The binding affinities of the double mutants are shown in Example 2, Table III, pages 38 - 42. Example 2 shows that the variants have significantly reduced binding affinities for IGFBP-1, but retain the same binding affinity to IGFBP-3 as the wild-type IGF-1. Example 2 further describes the KIRA assay of IGF-I type receptor activation and shows that the variants maintain the ability to activate the IGF-I receptor. Therefore, the variants are fully biologically active. Example 2 also shows that the variant F49A and the E3A.F49A double mutant accumulate at higher levels in the kidneys of rats

compared to wild-type IGF-I. The specification states that this would be beneficial for renal failure.

Use of wild-type IGF-I to treat mammals suffering from kidney disorders, renal dysplasias, and /or renal hypoplasias is described in U.S. Patent No. 5,985,830. Applicants rely on U.S. Patent No. 5,565,428 and 5,741,776 as teaching various methods of administration and dosages of wild-type IGF-I to treat human patients for a broad range of diseases. Accordingly, an IGF-I variant of the instant invention could be administered by these methods.

Thus one of skill in the art would be able to predict from the instant specification that an IGF-I variant recited in the claims would be able to increase the level of active IGF-I in a mammal.

The Office Action states that the state of the art teaches that activated IGF-I and its receptor display mitogenic, transforming and anti-apoptotic properties and that high circulating levels of IGF-I are positively associated with risk of prostate cancer and breast cancer.

The Office has not indicated how these studies/references are relevant to the claimed invention. The claimed invention is directed to increasing the levels of active IGF-I in mammals with low active IGF-I levels. Absent an indication of how these references are pertinent, Applicants request withdrawal of this rejection.

The Office Action states that the present invention is unpredictable and complex because the specification indicates that the concentration of IGF-I in the blood reach a plateau (page 42, lines 31-33 and page 43, lines 11-13).

Applicant notes that the section identified by the Examiner refers to WO98/45427 which describes the effect of the administration of wild-type IGF-I to the level of IGF-I concentration in the blood. Figure 42 of WO98/45427 shows that administration of wild-type IGF-I increases the level of active IGF-I in the blood until the level reaches a plateau. Clearly administration of wild-type IGF-I increases the concentrations of active IGF-I. Applicants fail to see why the fact that the level reaches a plateau is relevant to the claimed invention. Absent an indication of why

reaching a plateau renders the claimed invention complex and unpredictable, Applicants request withdrawal of this rejection.

For the above reasons, Applicants maintain that their specification is fully enabling for the claimed invention. Withdrawal of this rejection is respectfully requested.

CONCLUSION

For the reasons set forth above, Applicants believe that all claims are in condition for allowance. Should the Examiner believe that a telephone interview would expedite the prosecution of this application, Applicants invite the Examiner to call the undersigned attorney at the telephone number indicated below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referring to Attorney's Docket No. **39766-0131 R1-1D1**.

Respectfully submitted,

Dated: June 29, 2005 By: Leslie Mooi

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